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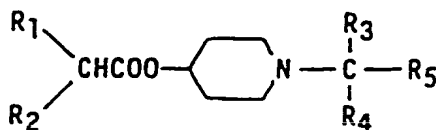
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(54) Title: 4-ACETOXY-PIPERIDINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND USE AS A MUS-
CARINIC M3-RECEPTOR ANTAGONIST

(I)

(57) Abstract

Compounds of formula (I), in which R₁ and R₂ are each separately selected from a phenyl group which is unsubstituted or substituted by one or more groups selected from alkyl, alkoxy, alkylendioxy, halogeno, halogeno substituted alkyl, hydroxy and nitro, R₃ and R₄ are each hydrogen or together are an oxo group and R₅ is an aromatic group, the compound optionally being in the form of a physiologically acceptable acid addition or quaternary ammonium salt, are of value as selective antagonists of the M₃ muscarinic receptor.

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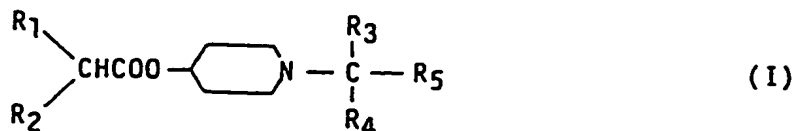
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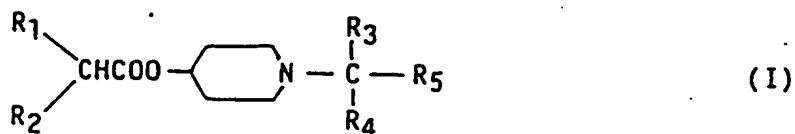
Accordingly the present invention comprises a compound of formula (I)



in which R_1 and R_2 are each separately selected from a phenyl group which is unsubstituted or substituted by one or more groups
 05 selected from alkyl, alkoxy, alkylenedioxy, halogeno, halogeno substituted alkyl, hydroxy and nitro, R_3 and R_4 are each hydrogen or together are an oxo group and R_5 is an aromatic group, the compound optionally being in the form of a physiologically
 10 acceptable acid addition or quaternary ammonium salt, for use in therapy.

These compounds are novel apart from the disclosure of 1-benzyl-4-diphenylacetoxypiperidine hydrochloride as an intermediate in Example 5 of European Patent Application A-0309424.

The present invention therefore further comprises a compound of
 15 formula (I)



in which R_1 and R_2 are each separately selected from a phenyl group which is unsubstituted or substituted by one or more groups
 20 selected from alkyl, alkoxy, alkylenedioxy, halogeno, halogeno substituted alkyl, hydroxy and nitro, R_3 and R_4 are each hydrogen or together are an oxo group and R_5 is an aromatic group, the compound optionally being in the form of a physiologically
 25 acceptable acid addition or quaternary ammonium salt thereof, but excluding the compound in which $R_1 = R_2 = R_5 = \text{phenyl}$ and $R_3 = R_4 = \text{hydrogen}$ and physiologically acceptable acid addition salts thereof.

4-acetoxy-piperidine derivatives, process for their preparation and use as a muscarinic M3-receptor antagonist.

This invention relates to esters of N-substituted piperidin-4-ols and to their use as therapeutic agents.


Studies have been reported in the literature on the activity of large numbers of esters of N-substituted piperidin-4-ols as
05 antimuscarinic drugs. Several muscarinic receptors exist, those concerned with actions at atria now being classified as M₂ and those concerned with the contraction of ileum now being classified as M₃. There is a particular need for compounds which show selective activity between the M₂ and M₃ receptors in order to
10 provide drugs which have activity at the M₃ receptor but with a significantly lower activity at the M₂ receptor, thereby reducing the level of undesirable side effects on the heart.

The search for suitable selective antagonists at the M₂ and M₃ receptors has continued for many years as indicated by Barlow and
15 Shepherd, Br. J. Pharmac., 1986, 89, 837-843, who describe further attempts to produce alternative antagonists to 4-diphenylacetoxy-N-methylpiperidine(4-DAMP) methobromide. However, it has now been found that a group of N-substituted 4-piperidinol esters possesses fully acceptable levels of antimuscarinic activity and shows
20 enhanced activity for the M₃ receptors as compared with the M₂ receptors, with a level of selectivity which in general is better than that of 4-DAMP methobromide. This group of compounds has never previously been studied as antimuscarinic drugs, although one compound is reported as an intermediate, only, in a patent
25 application relating to such drugs.

A finding in a compound of such selectivity is of greater value than a finding of enhanced, but non-selective, anti-muscarinic receptor activity for a new compound. Thus, the comprehensive
30 literature on antimuscarinic N-substituted piperidin-4-ol esters includes the studies reported by Sugai et al (Chem. Pharm. Bull., 1984, 32(3), 967 and 977, and Japanese Patent Application Number 27570/1979) on tertiary bases and quaternary ammonium salts which contain a substituted or unsubstituted 1,3-dioxolan-4-ylmethyl group substituted on the nitrogen atom of the piperidine ring.

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Particularly suitable substituents on a substituted phenyl group R_1 or R_2 are C_{1-6} alkyl groups, for example methyl, ethyl, propyl and isopropyl, C_{1-6} alkoxy groups, for example methoxy and ethoxy, C_{1-3} alkylenedioxy groups, for example methylenedioxy, fluoro, chloro, bromo and iodo groups, C_{1-6} alkyl groups substituted by one or more halogeno groups, for example three fluoro groups as in trifluoromethyl, hydroxy and nitro. Although various numbers of substituents may be present, for example 1, 2 or 3 monovalent substituents, preferably such substituted phenyl groups contain no more than one substituent (including one alkylenedioxy group) and conveniently the groups R_1 and R_2 are identical, especially with each being an unsubstituted phenyl group.

Although the grouping $-C(R_3)(R_4)-R_5$ may be an acyl group it is preferred that R_3 and R_4 are each hydrogen rather than together being an oxo group. The aromatic group R_5 may be carbocyclic or heterocyclic and unsubstituted or substituted, suitable heterocyclic groups consisting of a 5- or 6-membered ring system which contains one or two hetero atoms selected from the group consisting of oxygen, nitrogen and sulphur. Although suitable carbocyclic groups R_5 are both phenyl and naphthyl, it is generally preferred that R_5 is monocyclic. Moreover, it is further preferred that R_5 is a non-basic aromatic group so that among the heterocyclic groups thienyl is of greater interest than basic groups such as pyridyl, pyrimidyl, oxazolyl and thiazolyl, although such groups can be used as evidenced by the data presented herein on the compound containing a 2-pyridyl group R_5 . Preferred groups R_5 are thus 2- or 3-thienyl (thienyl indicates the univalent radical  derived from thiophene) and especially phenyl.

Such aromatic groups R_5 may be substituted by one or more substituents but preferably no more than one substituent, especially in the case of naphthyl and particularly of phenyl groups. Suitable substituents are broadly as described above for the substituted phenyl groups R_1 and R_2 , for example methyl, methoxy, fluoro and nitro. However, in the case of R_5 , halogeno

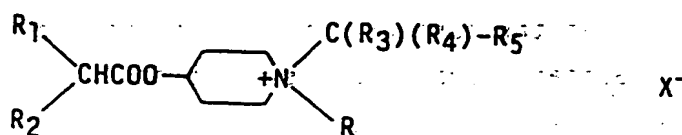
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and especially fluoro substituents are of the greatest interest. Substitution may be present at various positions in the ring but in the case of substituted phenyl groups there is particular interest in substitution at the ortho and especially the para positions, substitution at the meta position being less preferred, especially in the case of a nitro group. Unsubstituted groups R_5 are, however, generally preferred.

Specific compounds (I) according to the present invention are 4-diphenylacetoxy-1-phenacylpiperidine ($R_1 = R_2 = R_5 = C_6H_5$, $R_3 + R_4 = O$), 1-benzyl-4-diphenylacetoxypiperidine ($R_1 = R_2 = R_5 = C_6H_5$, $R_3 = R_4 = H$), 4-diphenylacetoxy-1-(2-thienylmethyl)-piperidine ($R_1 = R_2 = C_6H_5$, $R_3 = R_4 = H$, $R_5 = 2-C_4H_3S$) and 4-diphenylacetoxy-1-(3-thienylmethyl)-piperidine ($R_1 = R_2 = C_6H_5$, $R_3 = R_4 = H$, $R_5 = 2-C_4H_3S$).

As indicated, the tertiary bases (I) can be used in the form of physiologically acceptable salts which may be formed with various suitable inorganic and organic acids. Examples of such inorganic acids are phosphonic acid, nitric acid, sulphuric acid and particularly the hydrohalic acids hydrochloric acid, hydrobromic acid and hydroiodic acid. Examples of such organic acids are citric acid, oxalic acid, fumaric acid, maleic acid, lactic acid, succinic acid, malic acid, tartaric acid and methane sulphonic acid.

Formation of such an acid addition salt provides a particularly suitable method of formulating the basic compounds (I). In addition, however, it is possible to prepare quaternary ammonium salts in which the nitrogen atom of the piperidine ring is substituted by an additional group R to provide a salt as shown below in which a cation (Ia) is associated with one of various physiologically acceptable anions X^- .



(Ia)

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An alternative route to the compounds of formula (I) involves reacting a compound of formula (IV)



in which R_1 and R_2 are as defined for the compound of formula (I) or are groups convertible thereto, and Y is a suitable leaving group, with a compound of formula (V)



in which R_3 and R_4 are as defined for the compound of formula (I) and R_5 is as defined for the compound of formula (I) or is a group convertible thereto. Y is in particular a halogeno group, for example a bromo or especially a chloro group, or alternatively an alkoxy group, for example one containing an alkyl group as described hereinbefore in relation to alkyl substituents on substituted phenyl groups R_1 and R_2 , such as methoxy. The reaction is conveniently effected in solution in a suitable organic solvent such as toluene using an appropriate temperature and time, for example at 80°C over a period of up to 24 hours.

The free bases (I) often do not form crystalline solids and it is therefore usually convenient to isolate the compound (I) in the form of an acid addition salt by reaction with an acid, for example a monobasic acid. It is also usually preferable to formulate the compound (I) as a salt, for example with one of the acids described hereinbefore, for example HBr or HCl, and in such an instance the compound may suitably be isolated directly in the form of the acid addition salt which is to be used therapeutically.

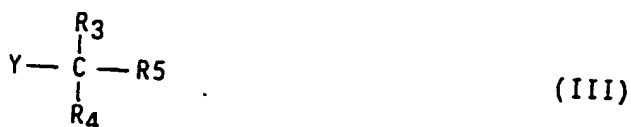
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The quaternary salts may contain a variety of groups RX but particularly preferred are those which contain a group R which is an alkyl group substituted by a phenyl group which may optionally itself be substituted, for example as described in relation to the groups R₁ and R₂, and particularly those which contain a group R which is an alkyl group. Such alkyl groups R may conveniently be as described hereinbefore in relation to alkyl substituents on substituted phenyl groups R₁ and R₂, for example being isopropyl, propyl, ethyl or particularly methyl. The group X may be of a variety of types, for example corresponding to the anions present in the acid addition salts described hereinbefore. Preferred groups X are however the halogeno groups, for example bromo or chloro.

The compounds of formula (I) are most conveniently prepared by reaction of a compound of formula (II)



in which R₁ and R₂ are as defined for the compound of formula (I) or are groups convertible thereto, with a compound of formula (III).



in which R₃ and R₄ are as defined for the compound of formula (I) and R₅ is as defined for the compound of formula (I) or is a group convertible thereto, and Y is a suitable leaving group, in particular a halogeno group, for example a chloro or especially a bromo group. The reaction is conveniently effected in solution in a suitable organic solvent such as chloroform using an appropriate temperature and time, for example at room temperature over a period of up to 24 hours.

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As an alternative to the use of the compounds (I) as the free base or an acid addition salt they may be formulated as a quaternary ammonium salt containing a cation (Ia) as indicated hereinbefore, although such salts do have disadvantages in terms of oral absorption and ability to cross the blood brain barrier. Such salts may conveniently be formed in several ways. Firstly the compound (I) may be reacted with a compound RX in which R is the additional group present on the nitrogen atom in the quaternary ammonium salt and X⁻ is the anion present therein. Alternatively a compound of formula (IIa)



in which R₁ and R₂ are as defined above for formula (II) and R is the additional group present in the quaternary ammonium salt may be reacted with a compound of formula (IIIa)



in which R₃, R₄ and R₅ are as defined above for formula (III) and X provides the anion present in the quaternary ammonium salt.

Particularly where the quaternary ammonium salts contain an anion which is not a halogeno anion, it may be convenient to prepare the salt by reaction of a quaternary ammonium salt containing such a halogeno anion with an alkali metal salt, for example a sodium or potassium salt, containing the alternative anion which it is desired to introduce.

Most commonly R₁, R₂ and R₅ in the compounds of formulae (II), (IV), (V), (III), (IIa) and (IIIa) are identical with those groups in the compound of formula (I) but in some instances it may be convenient for this not to be the case, particularly where these

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groups are substituted groups and the compounds (II) to (V), (IIa) and (IIIa) contain a substituent or substituents convertible to those present in (I).

05 It will be appreciated that the invention encompasses
compounds (I) in the various stereochemical forms in which they
exist, certain of which may be of particular value by virtue of
their level of therapeutic activity and/or physical properties such
as greater aqueous solubility, etc. In particular, when R₁ and R₂
are different the compounds will contain at least one asymmetric
10 carbon atom and will be resolvable into optically active isomers.
Moreover the quaternary ammonium salts can exist in different
stereoisomeric forms depending on the relative orientation of the
groups -C(R₃)(R₄)-R₅ and R to the rest of the molecule. Such
stereochemistry is described in detail by Sugai et al, ibid,
15 particularly in the Japanese patent application. It will be
appreciated, however, that the absence of stereoisomerism in a
compound (I) can simplify synthetic procedures and for that reason
free bases and acid addition salts (I) in which R₁ and R₂ are
identical and which do not contain other asymmetric carbon atoms
20 have an advantage.

The antagonist activity of the compounds of the present
invention against the muscarinic receptors, particularly against
the M₃ receptor, renders them of value as spasmolytics (or
antispasmodics) which may be used in the treatment of patients with
25 various conditions in which smooth muscle is in spasm. Such
conditions include gastrointestinal motility disorders such as the
spastic condition of the gut, functional diarrhoea, irritable bowel
syndrome, cardiospasm, pylorospasm, gastro-oesophageal reflux,
gastric and duodenal ulcers and also spasm of the biliary and
30 particularly urinary tracts and urinary incontinence. In addition
the compounds are of interest in the control of bronchospasm as M₃
receptors are involved in cholinergic-induced bronchoconstriction.

- 10 -

Other forms of administration than by injection or through the oral route may also be considered in both human and veterinary contexts, for example the use of suppositories or pessaries.

05 Another form of pharmaceutical composition is one for buccal or nasal administration, for example lozenges, nose drops or an aerosol spray, or alternatively drops for administration into the eye which may conveniently contain a sterile liquid diluent or carrier.

10 Thus, the invention further includes a pharmaceutical composition comprising a compound (I) as defined hereinbefore together with a physiologically acceptable diluent or carrier.

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions each comprising a unit dose, or a multiple or sub-multiple of a unit dose. Whilst the dosage of
15 active compound given will depend on various factors, including the particular compound which is employed in the composition and the condition treated, it may be stated by way of guidance that a satisfactory spasmolytic effect will often be achieved using a daily dosage of about 0.05 to 40 mg/kg, particularly of about 0.1
20 to 10 or 20 mg/kg, for example about 1 or 1.5 mg/kg. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. Where desired, more than one compound (I) may be administered in the pharmaceutical composition or, indeed, other
25 active compounds may be included in the composition.

The present invention therefore includes a compound of formula (I) as defined hereinbefore for use in therapy and also a method for the treatment of a patient in need of anti-spasmodic treatment which comprises administering to said patient a
30 therapeutically effective amount of a compound of formula (I) as defined hereinbefore.

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The particular value of the compounds is their ability to block effects on M₃ receptors in concentrations which do not have substantial effects on the beating of the heart. The compounds are of further interest for their anti-secretory activity and in addition to their effects on gastric and intestinal secretion therefore have potential for use in reducing nasal secretion in colds, in reducing sweating and for reducing excessive excretions in conjunction with operative procedures. Thus there is a role for cardiac-sparing substitutes for atropine as pre-operative medication, particularly in the elderly, and in preparations for suppressing nasal secretions and for reducing sweating.

It should also be noted that other antimuscarinics have been shown to be of value by virtue of a centrally acting effect in the treatment of defects of the central nervous system where the cholinergic or muscarinic mechanisms are malfunctioning, for example Parkinson's and Alzheimer's diseases and other conditions involving cognitive deficiencies. The compounds of the present invention thus have further potential in this area.

The compounds (I) may be formulated with a physiologically acceptable diluent or carrier for use as pharmaceuticals for veterinary, for example in an avian or especially a mammalian context, and particularly for human use by a variety of methods. For instance, they may be applied as a composition incorporating a liquid diluent or carrier, for example an aqueous or oily solution, suspension or emulsion, which may often be employed in injectable form for parenteral administration and therefore may conveniently be sterile and pyrogen free. Oral administration may also be used, particularly in the case of the free bases and their acid addition salts, and indeed is preferred. Although compositions for this purpose may incorporate a liquid diluent or carrier, it is more usual to use a solid, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. Such solid compositions may conveniently be of a formed type, for example as tablets, capsules (including spansules), etc.

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(B) The above procedure can be varied slightly so that in the case of the compound containing a 2-pyridyl group R₅ the reactant 2-chloromethylpyridine may be used as follows.

05 4-(Diphenylacetoxy)piperidine (2.37 g, 8.03 mmol), potassium carbonate (2.222 g, 16.1 mmol), 2-(chloromethyl)pyridine hydrochloride (1.31 g, 7.99 mmol) and catalytic sodium iodide (65 mg) are stirred together in boiling acetonitrile (30 ml) for 15 hours. The solvent is evaporated under reduced pressure. The residue is partitioned between water (30 ml) and chloroform
10 (3 x 50 ml). The combined organic portions are dried over sodium sulphate and the solvent is evaporated under reduced pressure. The residue is "flash" chromatographed on silica eluting with acetone-petrol (bp 40-60°C) 1/1 to give the free base as a pale yellow solid. This is dissolved in acetone (20 ml) and treated
15 with 48% HBr aqueous solution (1 ml). The solvents are evaporated under reduced pressure and the residue is co-evaporated under reduced pressure with toluene (30 ml). The residue is recrystallised from ethanol to give the 4-(diphenylacetoxy)-1-(2-pyridylmethyl)piperidine bis-hydrobromide salt as a white powder
20 (2.15 g).


A similar variation may be used with other compounds.

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The invention is illustrated by the following Examples.

EXAMPLES

Example 1 : Preparation of compounds (I)

05 (A) The compounds are prepared by reacting equimolar amounts of
the appropriate unsubstituted or substituted 4-diphenylacetoxy-
piperidine free base R_1R_2CHCOO -NH and the appropriate bromo
10 compound $Br-C(R_3)(R_4)-R_5$. The reactants are dissolved in
chloroform and stirred at room temperature overnight. The solution
is then washed with saturated aqueous sodium carbonate and the
chloroform layer is dried with magnesium sulphate. After
15 filtration, the solvent is distilled off, the last traces of
chloroform being removed by evaporation with ethanol. The residue
is triturated with ether and this often yields the base as a white
powder. The product from the trituration is dissolved in a mixture
of acetone and ether (3:1 by volume) and a slight excess of 50%
20 aqueous HBr is added with stirring. Stirring of the mixture is
continued overnight, the hydrobromide of the base often appearing
after only about 5 minutes as a white solid. The mixture is then
filtered and the solid washed with ether and recrystallized usually
from butanone or mixtures of butanone and ethanol with the addition
of ether if necessary.

Details of the crystallization solvent and melting point for
fourteen compounds (I) prepared in this way are given in Table 1.
These contain as R_5 a substituted or unsubstituted phenyl group, an
25 α - or β -naphthyl group or a 2- or 3-thienyl group. In addition
similar data on a fifteenth compound containing a 2-pyridyl group
 R_5 prepared as described under (B) below is also given in the
table. In the case of compound 7 the free base was obtained by
crystallization from ethanol/water of the product obtained by
30 trituration of the reaction residue. In the case of compound 2 the
methobromide was formed by reaction of the free base in butanone
with an excess (>1 equivalent) of methyl bromide.

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Example 2 : Comparison of activity of compounds (I) against
guinea-pig isolated atria and ileum

The procedures used were essentially those described by Barlow and Shepherd, Br. J. Pharmac., 1986, 89, 837-843 as indicated below.

05 (a) Guinea-pig isolated ileum

The guinea-pig ileum responses were recorded isotonicly with a load of about 0.5 g. The agonist, carbachol, was allowed to act for 30 seconds and added once every 90 seconds by relays controlled from a PET microcomputer. The tissue was suspended in Krebs
10 solution aerated with a mixture of 95% O₂ and 5% CO₂, usually containing 5 μ M norphenylephrine and experiments were carried out at 29.8 \pm 0.3°C.

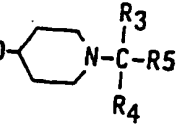
Alternate small and large control responses were obtained, usually to 0.1 and 0.2 μ M carbachol. When these were regular the
15 tissue was exposed to a solution of the antagonist and the concentration of agonist was increased to try to obtain responses which roughly matched the controls. When these were regular the approximate dose-ratio was given by the ratio of the concentrations of agonist used in the presence and in the absence of the antagonist
20 and an exact dose-ratio was calculated from the size of the responses by a calculation similar to a 4-point assay.

(b) Guinea-pig isolated atria

The atria were set up in Krebs solution aerated with a mixture of 95% O₂ and 5% CO₂, usually containing 5 μ M norphenylephrine (the
25 same solution as was used for the ileum). The temperature was 29.8 \pm 0.3°C and the spontaneous contractions were recorded isometrically with a load of about 0.2 g, action potentials also being recorded.

The agonist, carbachol, was added by relays operated from a
30 Commodore 128 microcomputer and allowed to act for 5 minutes. Doses were given once every 15 minutes with a second wash 10 minutes from the start of the cycle. The effects of the agonist were expressed as the percentage inhibition of the force of the contraction. As in the experiments on the ileum, the control responses were usually
35 obtained with 0.1 and 0.2 μ M carbachol. The tissue was then exposed to the antagonist and the experiment continued as with the ileum.

Table 1

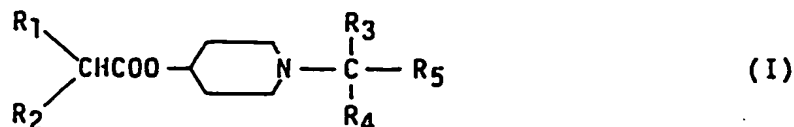
Compounds of formula $(C_6H_5)_2CHCOO-$  $N-C(R_3)(R_4)R_5$

Compound	R ₃ , R ₄	R ₅	Salt	M.p. °C	crystallization solvent
1	H, H	C ₆ H ₅	HBr	194.2	butanone/ ethanol/ether
2	H, H	C ₆ H ₅	CH ₃ Br	195.5	"
3	H, H	α-C ₁₀ H ₇	HBr	189.6	"
4	H, H	β-C ₁₀ H ₇	HBr	220.4	butanone/ethanol
5	H, H	2-C ₄ H ₃ S	HBr	192.8-193.2	"
6	H, H	3-C ₄ H ₃ S	HBr	175.5-176.2	butanone
7	H, H	p-CH ₃ -C ₆ H ₄	base	99.1	ethanol/water
8	H, H	o-F-C ₆ H ₄	HBr	176.3	butanone/ ethanol/ether
9	H, H	m-F-C ₆ H ₄	HBr	197.6	butanone/ethanol
10	H, H	p-F-C ₆ H ₄	HBr	186.5	"
11	H, H	m-NO ₂ -C ₆ H ₄	HBr	185.2	"
12	H, H	p-NO ₂ -C ₆ H ₄	HBr	not determined	butanone/ ethanol/ether
13	O=	C ₆ H ₅	HBr	not determined	butanone/ethanol
14	O=	m-CH ₃ O-C ₆ H ₄	HBr	206.7	"
15	H, H	2-C ₅ H ₄ N	2HBr	199.6-201.0	ethanol

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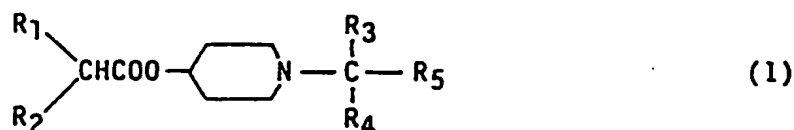
CLAIMS

1. A compound of formula (I)



in which R_1 and R_2 are each separately selected from a phenyl group which is unsubstituted or substituted by one or more groups selected from alkyl, alkoxy, alkylenedioxy, halogeno, halogeno substituted alkyl, hydroxy and nitro, R_3 and R_4 are each hydrogen or together are an oxo group and R_5 is an aromatic group, the compound optionally being in the form of a physiologically acceptable acid addition or quaternary ammonium salt, for use in therapy.

2. A compound of formula (I)



in which R_1 and R_2 are each separately selected from a phenyl group which is unsubstituted or substituted by one or more groups selected from alkyl, alkoxy, alkylenedioxy, halogeno, halogeno substituted alkyl, hydroxy and nitro, R_3 and R_4 are each hydrogen or together are an oxo group and R_5 is an aromatic group, the compound optionally being in the form of a physiologically acceptable acid addition or quaternary ammonium salt thereof, but excluding the compound in which $R_1 = R_2 = R_5 = \text{phenyl}$ and $R_3 = R_4 = \text{hydrogen}$ and physiologically acceptable acid addition salts thereof.

3. A compound according to Claim 1 or 2, in which R_5 is a phenyl or thienyl group which is unsubstituted or substituted by one or more groups selected from alkyl, alkoxy, alkylenedioxy, halogeno, halogeno substituted alkyl, hydroxy and nitro.

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The data obtained for the fourteen compounds (I) of Example 1 is given in Table 2. The dose-ratios obtained are used to calculate the affinity constants which are shown in log form. In some cases the mean estimate of log affinity constant, K, is shown (\pm s.e.) with the number of experiments carried out indicated in brackets. In the other cases only one experiment was carried out. It will be seen that for every compound there is a selective M₃ receptor antagonist effect with the effect against the atria being less than that against the ileum. On the basis of these results the highest level of selectivity was shown by 1-benzyl-4-diphenyl-acetoxypiperidine hydrobromide but nearly similar levels were shown by the hydrobromides of 1-(3-thienylmethyl)-4-diphenyl-acetoxypiperidine and particularly 1-(2-thienylmethyl)-4-diphenylacetoxypiperidine (compounds 1, 6 and 5 respectively).

Table 2
Atria and ileum log affinity constants for compounds (I)

Compound	Atria	Ileum
1	5.65 \pm 0.18 (4)	7.65 \pm 0.07 (5)
2	6.64 \pm 0.02 (4)	7.82 \pm 0.03 (5)
3	4.30	5.74
4	4.78	6.75
5	5.69 \pm 0.21 (2)	7.47 \pm 0.06 (3)
6	5.96 \pm 0.08 (3)	7.50 \pm 0.06 (3)
7	5.54	6.68
8	-	7.17
9	5.90	7.22, 7.46
10	5.48	7.07
11	5.70	6.48
12	5.87	7.07
13	6.03	6.87
14	5.26	6.12
15	5.07	7.10

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in which R_3 and R_4 are as defined for the compound of formula (I), R_5 is as defined for the compound of formula (I) or is a group convertible thereto, and Y is a suitable leaving group, and where appropriate in either order converting one or more of R_1 , R_2 and R_5 to the groups present in the compound (I) and/or converting the compound to an acid addition or quaternary ammonium salt:

(2) reacting a compound of formula (IV)



in which R_1 and R_2 are as defined for the compound of formula (I), or are groups convertible thereto, and Y is a suitable leaving group, with a compound of formula (V)



in which R_3 and R_4 are as defined for the compound of formula (I) and R_5 is as defined for the compound of formula (I), or is a group convertible thereto, and where appropriate in either order converting one or more of R_1 , R_2 and R_5 to the groups present in the compound (I) and/or converting the compound to an acid addition or quaternary ammonium salt; or in the case of the preparation of a quaternary ammonium salt:

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4. A compound according to Claim 3, in which R_5 is phenyl, 2-thienyl or 3-thienyl.
5. A compound according to any of Claims 1 to 4, in which R_1 and R_2 are each phenyl.
- 05 6. A compound according to any of Claims 1 to 5, in which R_3 and R_4 are each hydrogen.
7. A compound according to Claim 1, which is 1-benzyl-4-diphenyl-acetoxypiperidine, 4-diphenylacetoxyl-(2-thienylmethyl)-piperidine or 4-diphenylacetoxyl-(3-thienylmethyl)-piperidine.
- 10 8. A compound according to Claim 2, which is 1-(2-thienylmethyl)-4-diphenylacetoxypiperidine or 1-(3-thienylmethyl)-4-diphenylacetoxypiperidine.
9. A compound according to any of the preceding claims, which is in the form of the free base or an acid addition salt.
- 15 10. A compound according to any of Claims 1 to 8, which is in the form of a quaternary ammonium salt wherein the additional group substituted on the nitrogen atom of the ring is an alkyl group.
11. A compound according to Claim 1 or 2, which is a quaternary ammonium salt of 1-benzyl-4-diphenylacetoxypiperidine,
- 20 4-diphenylacetoxyl-(2-thienylmethyl)-piperidine or 4-diphenylacetoxyl-(3-thienylmethyl)-piperidine having an additional methyl group substituted on the nitrogen atom of the ring.
12. A process for the preparation of a compound of formula (I) as defined in Claim 1 which comprises:
- 25 (1) reacting a compound of formula (II)



in which R_1 and R_2 are as defined for the compound of formula (I), or are groups convertible thereto, with a compound of formula (III)

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(3) reacting a compound of formula (IIa)



in which R_1 and R_2 are as defined above for formula (II) and R is the additional group present in the quaternary ammonium salt with a compound of formula (IIIa)

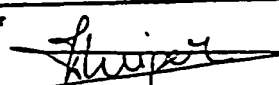


- 05 in which R_3 , R_4 and R_5 are as defined above for formula (III) and X provides the anion present in the quaternary ammonium salt, and where appropriate converting one or more of R_1 , R_2 and R_5 to the groups present in the compound (I); or
- 10 (4) reacting a quaternary ammonium salt produced by any of the three procedures with an alkali metal salt to replace the anion present in the quaternary ammonium salt by that present in the alkali metal salt and where appropriate converting one or more of R_1 , R_2 and R_5 to the groups present in the compound (I).
13. A process according to Claim 12, in which the procedure (1),
- 15 (3) or (4) is used.
14. A pharmaceutical composition comprising a compound of formula (I) as defined in any of Claims 1 to 11, together with a physiologically acceptable diluent or carrier.
- 20 15. A method for the treatment of a patient in need of anti-spasmodic treatment which comprises administering to said patient a therapeutically effective amount of a compound of formula (I) as defined in any of Claims 1 to 11.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/01810

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl.5 A 61 K 31/445	C 07 D 211/46	C 07 D 401/06 C 07 D 409/06
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 D A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0309424 (ISTITUTO DE ANGELI) 29 March 1989, see example 5 (cited in the application) ---	1-7,9,12
A	Journal of Medicinal Chemistry, vol. 8, no. 5, September 1965, Washington (US), C.R. Ganellin et al.: "Compounds affecting the central nervous system. I. 4-piperidones and related compounds", pages 619-625, see the whole article, table I ---	1-14
A	Chemical and Pharmaceutical Bulletin, vol. 32, no. 3, 3 March 1984, Tokyo (JP), S. Sugai et al.: "Studies on spasmolytics. I. Synthesis and spasmolytic activities of 4-acyloxy-1(1,3-dioxolan-4-ylmethyl)piperidines" pages 967-976, see the whole article, chart 1 (cited in the application) -----	1,14
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
29-01-1992	12 FEB 1992	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	Mme N. KUIPER 	

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SA 52302

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 15 because they relate to subject matter not required to be searched by this Authority, namely:
 Remark: Although claim 15 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claim numbers 1,2,5,6,9,10,12-14 /searched incompletely because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:
 The phrase "aromatic group" (main claims 1,2) is not acceptable. Since the claims are only partly supported by the description the search was based upon the exemplified evidence (R5=phenyl, thienyl, pyridyl) given in the descriptive part of the application (Art. 6 and 15(3) PCT). Nonetheless, the on-line search is complete for all compounds of formula I (R5=undefined).
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.